Notice of Allowability	Application No.	Applicant(s)	
	09/974,619	SCHUETZ ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *amendment filed 7/15/2005*.

2. ☒ The allowed claim(s) is/are *1-12,23 and 26-32*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Kathleen Tyrell on September 29, 2005.

The application has been amended as follows:

Claim 8 (Amended): A method for determining the cytochrome P450 3A5 (CYP3A5) genotype and phenotype of an individual comprising:

(a) isolating nucleic acid from the individual;

(b) amplifying a region of the cytochrome P450 3A5 (CYP3A5) gene sequence selected from the group of:

(i) intron 3 comprising the position corresponding to nucleotide 23 of SEQ IDNO:73;

(ii) exon 7 comprising the position corresponding to nucleotide 29 of SEQ ID NO:74; and

(iii) intron 3 comprising the position corresponding to nucleotide of SEQ ID NO:73 and exon 7 comprising the position corresponding to nucleotide 29 of SEQ ID NO:74; and

(c) sequencing the amplified region of step (b), thereby determining the cytochrome P450 3A5 (CYP3AS) genotype and phenotype of the individual, wherein the cytochrome P450 3A5 phenotype is as follows:

wherein the presence of an A at the position corresponding to nucleotide 23 of SEQ ID NO:73 on at least one CYP3A5 allele of said subject is indicative of a relatively high level of expression of CYP3A5 as compared to the presence of a G at that position; or the presence of a G at the position corresponding to nucleotide 23 of SEQ ID NO:73 on each CYP3A5 allele of said subject is indicative of a relatively low level of expression of CYP3A5 as compared to the presence of an A at that position; or

wherein the presence of a G at the position corresponding to nucleotide 29 of SEQ ID NO:74 on at least one CYP3A5 allele of said subject is indicative of a relatively high level of expression of CYP3A5 as compared to the presence of an A at that position; or

the presence of an A at the position corresponding to nucleotide 29 of SEQ ID NO:74 on each CYP3A5 allele of said subject is indicative of a relatively low level of expression of CYP3A5 as compared to the presence of a G at that position; or

wherein the presence of an A at the position corresponding to nucleotide 23 of SEQ ID NO:73 and a G at the position corresponding to nucleotide 29 of SEQ ID NO:74 on at least one CYP3A5 allele of said subject is indicative of a relatively high level of expression of CYP3A5 as compared to the presence of a G at the position corresponding to nucleotide 23 of SEQ ID NO:73 and an A at the position corresponding to nucleotide 29 of SEQ ID NO:74 on at least one CYP3A5 allele of said subject; or the presence of either a G at the position corresponding to nucleotide 23 of SEQ ID NO:73 or an A at the position corresponding to nucleotide 29 of SEQ

ID NO:74 on each CYP3A5 allele of said subject is indicative of a relatively low level of expression of CYP3A5 as compared to the presence of either an A at the position corresponding to nucleotide 23 of SEQ ID NO:73 or a G at the position corresponding to nucleotide 29 of SEQ ID NO:74 on each CYP3A5 allele of said subject.

Claim 10: (Amended) The method of claim 9 wherein the intron 3 region is amplified utilizing [SEQ ID NO: 24 and 25 primers or a fragment thereof which is at least ten bases long, or SEQ ID NO: 26 or 27 primers, or a fragment thereof which is at least ten bases long] a set of primers, wherein said set of primers contains primer X and primer Y; wherein

i) primer X has the sequence of SEQ ID NO: 24, or a fragment thereof which is at least ten nucleotides long; and primer Y has the sequence of SEQ ID NO: 25, or a fragment thereof which is at least ten nucleotides long; or

ii) primer X has the sequence of SEQ ID NO: 26, or a fragment thereof which is at least ten nucleotides long, and primer Y has the sequence of SEQ ID NO: 27, or a fragment thereof which is at least ten nucleotides long.

Claim 12: (Amended) The method of claim 11 wherein the exon 7 region is amplified utilizing [SEQ ID NO: 30 and 16 primers, or a fragment thereof which is at least ten bases long, or SEQ ID NO: 31 or 32 primers, or a fragment thereof which is at least ten bases long] a set of primers, wherein said set of primers contains primer X and primer Y; wherein

i) primer X has the sequence of SEQ ID NO: 30, or a fragment thereof which is at least ten nucleotides long; and primer Y has the sequence of SEQ ID NO: 16, or a fragment thereof which is at least ten nucleotides long; or

ii) primer X has the sequence of SEQ ID NO: 31, or a fragment thereof which is at least ten nucleotides long, and primer Y has the sequence of SEQ ID NO: 32, or a fragment thereof which is at least ten nucleotides long.

Claim 23 (Amended) A method of determining cytochrome P450 3A5 (CYP3A5) genotype of a subject which comprises

(a) isolating nucleic acid from said subject;

(b) amplifying a cytochrome P450 3A5 (CYP3A5) PCR fragment from said nucleic acid using a set of primers, wherein said set of primers contains primer X and primer Y; wherein

i) primer X has the sequence of SEQ ID NO: 30 [24], or a fragment thereof which is at least ten [bases] nucleotides long; and primer Y has the sequence of SEQ ID NO: 16 [25], or a fragment thereof which is at least ten [bases] nucleotides long; or

ii) primer X has the sequence of SEQ ID NO: 31 [26], or a fragment thereof which is at least ten [bases] nucleotides long, and primer Y has the sequence of SEQ ID NO: 32 [27], or a fragment thereof which is at least ten [bases] nucleotides long;

and the amplified cytochrome P450 3A5 (CYP3A5) PCR fragment is in between primers X and Y; and

(c) sequencing the amplified fragment obtained in step (b), thereby determining the cytochrome P450 3A5 (CYP3A5) exon 7 genotype of said subject.

Claim 27 (Amended) The method of claim 26 wherein the first primer introduces a *Tru9I/Mse*I restriction site in the presence of an A nucleotide at the position corresponding to nucleotide 29 of SEQ NO:74 in exon 7, and the second primer has the sequence selected from SEQ ID NO:32 and SEQ ID NO:16, or a fragment thereof which is at least ten [bases] nucleotides long.

Claims 28 (Amended) The method of claim 26 wherein the first primer has the sequence of SEQ ID NO: 34, or a fragment thereof which is at least ten [bases] nucleotides long, and the second primer has the sequence of SEQ ID NO: 32, or a fragment thereof which is at least ten [bases] nucleotides long.

Claim 29 (Amended) The method of claim 26 wherein the first primer has the sequence of SEQ ID NO:34, or a fragment thereof which is at least ten [bases] nucleotides long, and the second primer has the sequence of SEQ ID NO:16, or a fragment thereof which is at least ten [bases] nucleotides long.

Claim 31 (Amended) The method of claim 30 wherein primer X has the sequence of SEQ ID NO:30, or a fragment thereof which is at least ten [bases] nucleotides long; primer Y has the sequence of SEQ ID NO: 16, or a fragment thereof which is at least ten [bases] nucleotides long; primer Z introduces a *Tru9I/Mse*I restriction site in the presence of an A nucleotide at the position corresponding to nucleotide 29 of SEQ ID NO: 74 in exon 7; and primer W has the sequence selected from SEQ ID NO:32 and SEQ ID NO:16, or a fragment thereof which is at least ten [bases] nucleotides long.

Claim 32 (Amended) The method of claims 31 wherein primer Z has the sequence of SEQ ID NO: 34, or a fragment thereof which is at least ten [bases] nucleotides long.

REASONS FOR ALLOWANCE

2. The following is an examiner's statement of reasons for allowance:

Claims 1-7 are drawn to a method for predicting CYP3A5 expression level by determining the nucleotide present at the position corresponding to nucleotide 23 of SEQ ID NO: 73 within intron 3 of the CYP3A5 gene and/or the position corresponding to nucleotide 23 of SEQ ID NO: 74 within exon 7 of the CYP3A5 gene, wherein the CYP3A5 expression level is correlated with the identity of the nucleotide as set forth in the claims. Claims 8-12 are drawn to a method for determining the CYP3A5 genotype and phenotype of an individual by determining the nucleotide present at the position corresponding to nucleotide 23 of SEQ ID NO: 73 within intron 3 of the CYP3A5 gene and/or the position corresponding to nucleotide 23 of SEQ ID NO: 74 within exon 7 of the CYP3A5 gene, wherein the CYP3A5 phenotype is altered expression of CYP3A5 depending on the identity of the nucleotide as set forth in the claims. The closest prior art is the submission ss903337 in dbSNP of NCBI which teaches an A or G at the position corresponding to nucleotide 23 of SEQ ID NO: 73 within intron 3 of the CYP3A5 gene. The claims are allowable over the closest prior art because the prior art does not teach or suggest a change in expression level of CYP3A5 wherein an A at the position corresponding to nucleotide 23 of SEQ ID NO: 73 within intron 3 on at least one CYP3A5 allele of the subject predicts a relatively high level of expression of CYP3A5 as compared to the presence of a G at that position and the presence of a G at the position corresponding to nucleotide 23 of SEQ ID NO:

73 within intron 3 on each CYP3A5 allele of the subject predicts a relatively low level of expression of CYP3A5 as compared to the presence of an A at that position. Further, such altered expression as set forth in the specification at pages 63-64 is unexpected and not taught or suggested by the teaching of a SNP in the ss903337 submission or in references teaching sequencing of the CYP3A5 gene. Therefore, the claims are allowable over the unexpected result of detecting a particular CYP3A5 phenotype in a subject, altered CYP3A5 expression, by determining the identity of the SNP[s] at the position corresponding to nucleotide 23 of SEQ ID NO: 73 within intron 3 of the CYP3A5 gene. The prior art does not teach or suggest a polymorphism at the position corresponding to nucleotide 29 of SEQ ID NO: 74 of exon 7 of the CYP3A5 gene.

Claim 23 is drawn to a method of determining the CYP3A5 genotype of as subject using a set of primers wherein the first primer is SEQ ID NO: 30 or a fragment thereof which is at least 10 nucleotides long, and the second primer is SEQ ID NO: 16, or a thereof which is at least 10 nucleotide long; or wherein the first primer is SEQ ID NO: 31 or a fragment thereof which is at least 10 nucleotides long, and the second primer is SEQ ID NO: 32, or a fragment thereof which is at least 10 nucleotide long. Claims 26-32 are drawn to methods of determining the CYP3A5 genotype of as subject using primers which include a primer which introduces a base change adjacent to or near the position corresponding to nucleotide 29 of SEQ ID NO: 74 in exon 7 of the CYP3A5 gene such that a restriction site is generated in the presence of a particular nucleotide at the position corresponding to nucleotide 29 of SEQ ID NO: 74 in exon 7 (claims 26 and 30). The closest prior art is that of Genbank Accession number AC005020 and Smith which teach to sequence the CYP3A5 gene. The claims are allowable over the teachings of Genbank

Accession number AC005020 and Smith because the prior art does not teach or suggest use of the specific primers set forth in claim 23 or a primer with the specific properties as claimed in claims 26 and 30. As the prior art is silent with regard to a polymorphism at the position corresponding to nucleotide 29 of SEQ ID NO: 74 in exon 7 of the CYP3A5 gene, there is no motivation provided in the art to choose a primer which specifically introduces a base change adjacent to or near the position corresponding to nucleotide 29 of SEQ ID NO: 74 in exon 7 of the CYP3A5 gene such that a restriction site is generated in the presence of a particular nucleotide at the position corresponding to nucleotide 29 of SEQ ID NO: 74 in exon 7, or the primer pairs with the specific sequences as recited in claim 23.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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9/29/05